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Frequently, intraductal breast cancer (DCIS) presents only as calcifications without an associated mass. As DCIS represents as much as a third of mammographically detected cancer, it would be efficacious to image microcalcifications by as many modalities as possible in order to allow flexibility in image guided biopsies. We have developed a technique utilizing acoustic resonance to visualize microcalcifications under ultrasound. Our work with phantoms show that ultrasound coupled with acoustic resonance can reliably demonstrate small calcific particles for targeting and biopsy. After doing extensive evaluation with phantom models, we have begun evaluating and optimizing the technique of imaging breast microcalcifications with power Doppler and acoustic resonance using ultrasound in patients with breast microcalcifications prior to biopsy.

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Introduction:

It is estimated that ductal carcinoma in situ (DCIS) represents 20-30% of breast carcinomas detected on screening mammography (1). Since the 1970's the detection rate of ductal carcinoma in situ has steadily increased with the wider use of screening mammography. The detection rate for women less than 50 years of age was reported to be 2.3 cases per 100,000 women in the 1970's increasing to 6.2 cases per 100,000 women by the 1990's. More dramatically, in the group of women over the age of 50, the rate has increased from 14.3 to 54.6 per 100,000 (2) in the same time period. Frequently, DCIS presents only as calcifications without an associated mass. As DCIS represents as much as a third of mammographically detected cancer, it would be efficacious to image microcalcifications by as many modalities as possible in order to allow flexibility in image guided biopsies. Currently, even with all the technical advances in breast imaging, including magnetic resonance imaging, scintigraphy, and ultrasound, mammography is the only reliable method to detect, characterize and localize microcalcifications for biopsy. We have developed a technique utilizing acoustic resonance to visualize microcalcifications under ultrasound. The concept of acoustic resonance imaging (ARI) is based on the size of the microcalcifications and the binding strength with the surrounding tissues in which it is imbedded. When subjected to a wide frequency range, different sized particles will resonate at different frequencies given the same binding environment. By "tuning" into the appropriate frequency range, it would be possible to selectively visualize microcalcifications of varying sizes

Body:

Task1

At the writing of this report, we are approximately 9 ½ months into the project since the inception. The earliest part of the activity focused on the organizational aspects of the project. This included implementation of the plans for establishing the database and training for patient recruitment and approval of the study from the University Institutional Review Board. We have constructed a stand with a vibration device that connects into the ultrasound scanner to vibrate and image calcifications within the breast. This device is fully operational and dedicated completely to the project. The main component of this system consists of a board with a processor chip ADSP2181 (Analogic Devices). With the help of a special computer program loaded onto the EPROM of the chip on the DSP board signals 2 volts (peak to peak) are generated in the frequency range of 10 Hz to 20 kHz. The frequency of the vibration is stepped up at a regular interval of 30 milliseconds or it's multiple. Using this system the frequency of vibration is scanned at a known scale and known amplitude. The output from this device is used to drive the vibrations of the transducer through an amplifier. The DSP board also communicates with the video signal obtained directly from an ultrasound scanner. All the information related to the frequency and amplitude of the vibration device in encoded onto each video frame by co-registering the image and vibration data on video frames. We are able to synchronize the two modes of operation, i.e., the imaging and vibration of the breast.

Each resonance experiment generates a time series of images depicting vibration of calcium particles. Each scan takes approximately 1 minutes and 50 secs. At the video frame rate of 30 images per second, this generates approximately 110 x 30 = 3, 300 images. An algorithm was developed to reduce the data by sorting the images on the basis on frequency of vibration.

These images are subsequently used with a computer program developed in the ultrasound laboratory at the University of Pennsylvania to analyze the vibration response of the breast calcifications.

After initial organization and technical development, we focused on designing tissue mimicking phantoms and using these phantoms to evaluate the performance of the vibrational device. Several different approaches were tried for constructing the phantoms. Best results were obtained by using distilled water and gelatin in the ratio of 5 parts distilled water to 1 part gelatin. The mixture was heated to 50 degrees Celsius while stirring constantly. The mixture was maintained at this temperature till all the gelatin was dissolved. Special care was taken to avoid any frothing or bubble formation due to stirring. A small volume (2 ml/100 ml of this solution) of isopropyl alcohol was added to break small bubbles. The solution was allowed to cool to set the gelatin. The calcium particles from crushed chalk and seashells were imbedded in phantoms by controlled melting of regions within the phantom and dropping calcium particles into the melted area. These particles gradually sank as the overlying liquid solidified.

While the technique of phantom construction was successful and it allowed us to prepare the phantoms on a regular basis, there are two limitations that need further improvement. The first deals with the control of the size of the calcium particles. The sizes of the particles are measured before they are imbedded into the gelatin. Often these particles tend to aggregate together during the imbedding process thus leading to the formation of greater than the size of the original particle. Secondly, in theory, the precise frequency of resonance depends on the strength of binding between the calcium particles and the surrounding tissues. With our current approach, it is not yet been feasible to control the precise nature and strength of these bindings. As a result, the peak frequency of resonance exhibits variation from one sample to another. We

are in the process of evaluating if the purity of water and/or the nature of the gelatin used have a role to play.

The third phase of the program focused on using tissue-mimicking phantoms along with the gelatin phantoms to evaluate the phenomenon of acoustic resonance. The results of this study have been very successful and have been submitted for publication. Calcium carbonate particles imbedded in gelatin and turkey breast tissue were visualized using acoustic resonance imaging and power Doppler. Sonography revealed power Doppler detection corresponding to the location of the calcium carbonate particles. Correlation between power detection and the location of the calcium carbonate particles was confirmed with core needle biopsy of the area of power detection and specimen radiograph. A Bard 14 gauge disposable core biopsy needle (Bard Monopty Biopsy Instrument, C.R. Bard, Inc., Covington, GA) was used to biopsy the region of interest while scanning real time using power Doppler coupled with ARI. Multiple samples were obtained through the phantom in the region of maximum power detection. The core biopsy samples were placed in a container (Beekley Corporation, Bristol, CT) and x-rayed (Instrumentarium alpha RT, Milwaukee, WI) at 22 kvp and 6 mas with 1.8 x magnification to confirm that the biopsy target, the region of power Doppler detection, corresponded to the calcium carbonate particles.

The calcium carbonate particles were readily visible within the gelatin phantoms with the B-scan mode. With power Doppler evaluation, a trend of gradual increase in power detection was seen in the region of the calcium carbonate particles resulting in a maximum power level detection between the frequencies of $\approx$200 – 300 Hz followed by a gradual decrease. With the frequency fixed between $\approx$200-300, the area of maximal power detection was targeted and cored

using a disposable core biopsy device. The x-rayed samples demonstrated the presence of the calcium carbonate particles.

The turkey phantom was also ultrasounded in the B-scan mode and with power Doppler. Unlike in the gelatin phantom, the calcium carbonate particles were not easily visible in the B-scan mode in the turkey phantom. When power Doppler was used, a similar trend was seen as in the gelatin phantoms. Maximal power Doppler was detected at ≈200 Hz followed by a decrease. In the simple gelatin phantom, the microcalcifications are visible without power Doppler imaging, allowing for direct correlation between the location of the particles and the area of color level detection. Unlike the homogeneous background of the gelatin phantom, the turkey phantom model more closely approximates the human breast tissue with muscle striations and specular interfaces similar to the appearance of Cooper's ligaments and other specular reflectors in the human glandular tissue. Therefore, the location of the calcium carbonate particles is not obvious, until the power Doppler coupled with ARI is used. The area of power level detection was core biopsied in both types of phantoms, and x-rayed, confirming that it indeed corresponded to the calcium carbonate particles.

Task 2

We are currently in the process of implementing studies dealing with the evaluation of the technique in patients. Towards this task, we have implemented techniques for digitizing mammograms and analyzing Doppler images. This includes measuring MCL (the mean color level), percent area and color weighted fractional area. To date we have recruited 3 patients in this study. In the next 3 months, we hope to follow-up with recruiting more aggressively.

Our first goal was to identify optimal parameters for ultrasounding patients. Data from the turkey breasts phantoms with and without imbedded calcifications was used to provide initial guidance of these parameters.

Following imaging parameters for ultrasounding patients on with ATL 5000 ultrasound machine were identified

Imaging frequency: 12 megahertz

Echogain: 40%

Persistence of power Doppler images: medium

Grey scale map for imaging: Map 3

Mechanical index: 0.6

Color map for power Doppler: Map 1

Pulse repetition frequency (PRF): 1000

Wall filter for Doppler imaging: medium

Frame rate of imaging: ≥ 8 Hz

Following setting were identified for the vibration device

Start frequency: 50 hertz

End frequency: 600 hertz

Step size for frequency increment: 5 hertz

Interval of time increment: 1 sec (or 30 video frames)

In patient 1, several large calcifications were observed mammographically at the 11:00 location in the right breast. These calcifications were surrounded by smaller clusters of calcium particles. We were able to visualize these calcium particles on gray scale imaging. The resonance scans also revealed high sensitivity to other structures as well. At the low end of the frequency spectrum, 50-140 Hz some connective tissue close to calcifications also exhibited motion in response to the acoustic resonance. Since our goal of the study is to maximize visualization of the calcifications while decreasing the background noise, it was decided to decrease the gain of the imaging system and to reduce the vibration output for the next patient. On pathologic evaluation, the calcifications that were biopsied in this patient were benign.

The second patient recruited for this study had calcifications at the 2:00 location in the left breast. The area of calcifications had previously been biopsied percutaneously and a metallic clip had been left at biopsy site, which we believe would serve as a landmark and help in the identification of the site and validation of the technique. Unfortunately, no enhancement could be seen in the region of the calcifications with resonance imaging. We were also not able to locate the clip directly with the ultrasound. The lack of enhancement could be either because we decreased the gain of imaging of vibration of our system more than what was necessary. Second possible cause could be that imaging was not performed at the location of the calcification. Although, we use the mammographic images to guide us to the approximate location of the calcifications, due to significant differences in the geometry of the breast during mammographic and ultrasound examination, it is sometimes difficult to match the planes of imaging between the two modes. The biopsy results in this patient revealed ductal carcinoma in situ and invasive lobular carcinoma.

The third patient recruited for this study had fine calcifications in the superficial portion of the right breast. Scanning was performed using original imaging parameters. In this case enhancement of calcification was observed on the resonance scans. For quality control, we also ultrasounded an area in the breast that did not contain any microcalcifications using the identical parameters. Scanning of the region without calcifications showed no enhancement. Pathology results of the calcifications revealed ductal carcinoma insitu.

At the writing of this report, we believe we have not yet achieved optimal imaging parameters for scanning patients although the technique is effective in phantom models. There is greater tissue variability in patients, i.e. the amount of fatty and glandular breast tissue than in phantoms. In the next group of scans, we plan to focus on a better control angle between on the vibrational device and the transducer and optimize the gain settings.

Key Research Accomplishments:

- Designed gelatin and tissue phantom models to evaluate microcalcifications using ARI and power Doppler
- Obtained University IRB approval to implement the technique on patients
- Set up database for recording and analyzing data
- Began patient recruitment and evaluating/optimizing the technique on patients

Reportable Outcomes:

- The research results have been presented at the meeting of The Radiological Society of North America.
- Our manuscript, *Using Acoustic Resonance Coupled with Power Doppler Imaging to Visualize Microcalcifications in Breast Tissue Phantoms*, has been submitted to the journal Radiology and has been preliminarily accepted based on satisfactory revision.

Conclusions:

In summary, over the short duration of this project, we have made significant progress on the technical front in implementing the technique of visualizing microcalcifications using acoustic resonance and power Doppler and evaluating this technique on phantoms. While we will continue to conduct and improve phantom related studies, in the next phase of the program we plan to optimize and evaluate the technique in the patient population. Our goal is to assess if the calcifications can be readily visualized using acoustic resonance and power Doppler. Once visualized, we hope to analyze if the sonographic characteristics can aid us in differentiating the malignant from benign calcifications.

Reference:

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2. Ernster VL, Barclay J, Kerlikowske K, Wilkie H, Ballard-Barbash R. Mortality among women with ductal carcinoma in situ of the breast in the population-based surveillance, epidemiology and end results program. Arch Intern Med 2000;160:953-958.

Appendices:

See attached